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(54) Title: HYDROGENSULFATE SALT OF 2-ACETOXY-5-(a-CYCLOPROPYLCARBONYL-2-FLUOROBENZYL)-4,5,6,7-TETRAHYDROTHIENO[3,2-c]PYRIDINE AND ITS PREPARATION

(57) Abstract: The present invention relates to crystalline form I of Prasugrel hydrogensulfate. A process for the preparation of these salts, pharmaceutical compositions comprising the salts and the use of the salts as a pharmaceutical, in particular as a blood platelet aggregation inhibitor are also described. Seed crystals which can be employed in the above mentioned process as well as a process for their preparation are also disclosed.

HYDROGENSULFATE SALT OF 2-ACETOXY-5-(α-CYCLOPROPYLCARBONYL-2-FLUOROBENZYL)-4,5,6,7-TETRAHYDROTHIENO[3,2-c]PYRIDINE AND ITS PREPARATION

FIELD OF THE INVENTION

The present invention relates to crystalline form I of the hydrogensulfate salt of 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine. A process for the preparation of the salt, pharmaceutical compositions comprising the salt and the use of the salt as a pharmaceutical, in particular as a blood platelet aggregation inhibitor are also described. Seed crystals which can be employed in the above mentioned process as well as a process for their preparation are also disclosed.

BACKGROUND OF THE INVENTION

Prasugrel, 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine, is a thienopyridine derivative and acts as an antiplatelet agent. The platelet activation and subsequent platelet aggregation play an essential role in the pathogenesis of cardiovascular diseases. A former clinical study could demonstrate that Prasugrel is orally active and produces a potent antiplatelet and antithrombotic action with a rapid onset and long duration *via* platelet ADP receptors antagonisms. Prasugrel is a prodrug, which means it generates an active metabolite *in vivo* (Sugidachi A., Asai F., Ogawa T., et al., "The in vivo pharmacological profile of CS-747, a novel antiplatelet agent with platelet ADP receptor antagonist properties", Br. J. Pharmacol. 2000, **129**:1439-1446).

US 6,693,115 claims that acid addition salts of Prasugrel are useful as therapeutic or prophylactic agents for thrombus formation-induced or embolization-induced diseases. Prasugrel hydrochloride and Prasugrel maleate are disclosed in US 6,693,115. Furthermore a Prasugrel besylate is mentioned in WO 2007/114526.

Polymorphism is a phenomenon relating to the occurrence of different crystal forms for one molecule. There may be several different crystalline forms for the same molecule with distinct crystal structures and varying in physical properties like melting point, XRPD spectrum and IR-spectrum. These polymorphs are thus distinct solid forms which share the molecular

formula of the compound from which the crystals are made up, however they may have distinct advantageous physical properties which can have a direct effect on the ability to process and/or manufacture the drug substance, like flowability, and the drug product, like flowability, as well as on drug product stability, dissolution, and bioavailability.

There remains a need for alternative acid addition salts of Prasugrel having improved physicochemical properties.

Apart from permeability, solubility is the main criterion in the biopharmaceutical classification system. An optimal active pharmaceutical ingredient for oral application should show high solubility in the range from about pH 1.0 up to about pH 8.0, in order to show high bioavailability. Therefore it is desirable to have an acid addition salt of Prasugrel with suitable solubility in a broad pH-range.

SUMMARY OF THE INVENTION

In one embodiment, the present invention refers to crystalline form I of Prasugrel hydrogensulfate.

Crystalline form I of Prasugrel hydrogensulfate can be described by an X-ray powder diffraction pattern comprising peaks at 2-theta angles of 9.2 ± 0.2°, 13.1 ± 0.2°, 13.9 ± 0.2°, 14.8 ± 0.2°, 16.0 ± 0.2°, 17.0 ± 0.2°, 17.7 ± 0.2°, 18.9 ± 0.2°, 19.7 ± 0.2°, 21.2 ± 0.2°, 22.7 ± 0.2°, 25.1 ± 0.2° and 28.0 ± 0.2°.

Alternatively crystalline form I of Prasugrel hydrogensulfate can be described by an infrared spectrum comprising peaks at wavenumbers of 1751 ± 2 cm^{-1}, 1712 ± 2 cm^{-1}, 1495 ± 2 cm^{-1}, 1153 ± 2 cm^{-1}, 1060 ± 2 cm^{-1}, 858 ± 2 cm^{-1} and 774 ± 2 cm^{-1}.

In addition crystalline form I of Prasugrel hydrogensulfate can be described by a Raman spectrum comprising peaks at wavenumbers of 1616 ± 2 cm^{-1}, 1510 ± 2 cm^{-1}, 1444 ± 2 cm^{-1}, 1289 ± 2 cm^{-1}, 1231 ± 2 cm^{-1}, 1194 ± 2 cm^{-1}, 1021 ± 2 cm^{-1}, 871 ± 2 cm^{-1}, 812 ± 2 cm^{-1}, 778 ± 2 cm^{-1}, 709 ± 2 cm^{-1}, 580 ± 2 cm^{-1} and 539 ± 2 cm^{-1}.

A process for the preparation of crystalline form I of Prasugrel hydrogensulfate comprising the steps of:

(a) heating a mixture of Prasugrel or a salt or a derivative thereof, sulfuric acid and optionally a solvent to a temperature of about 35 °C or more;

(b) reducing the temperature of the mixture to about 30 °C or below;
(c) adding seed crystals; and
(d) isolating crystalline form I of Prasugrel hydrogensulfate

is also subject matter of the present invention.

Another aspect the present invention relates to a pharmaceutical composition comprising crystalline form I of Prasugrel hydrogensulfate as defined above and optionally a pharmaceutically acceptable carrier.

The pharmaceutical composition can be used for inhibiting blood platelet aggregation. In particular, it can be employed for treating or preventing a disorder selected from the group consisting of thrombosis, embolism, coagulation induced vascular diseases and recurrence thereof and for use as an adjunct to percutaneous coronary intervention procedures. Furthermore, it can be used for preventing atherothrombotic events after myocardial infarction, after stroke, in patients having established peripheral arterial disease or in patients having Acute Coronary Syndrome.

Crystalline form I of Prasugrel hydrogensulfate shows high solubility within a broad pH range. This property enables the manufacture of finished dosage forms which, due to the low solubility of the prior art Prasugrel hydrochloride or Prasugrel maleate, could not be prepared easily, like liquid aqueous preparations for oral use (e.g. oral solutions, oral emulsions, oral suspensions, powders and granules for oral solutions and suspensions, oral drops, powder for oral drops, syrups, powders and granules for syrups), soluble tablets and parenteral preparations (e.g. injections, infusions, concentrates for injections or infusions, powders for injections or infusions, gels for injections, implants).

Other objects, features, advantages and aspects of the present invention will become apparent to those of skill from the following description. It should be understood, however, that the description and the following specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only. Various changes and modifications within the spirit and scope of the disclosed invention will become readily apparent to those skilled in the art from reading the description and the other parts of the present disclosure.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: X-ray powder diffraction pattern of crystalline form I of Prasugrel hydrogensulfate

Figure 2: Infrared spectrum of crystalline form I of Prasugrel hydrogensulfate

Figure 3: Raman Spectrum of crystalline form I of Prasugrel hydrogensulfate

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to crystalline form I of Prasugrel hydrogensulfate.

The chemical structure of Prasugrel hydrogensulfate is shown in Figure A.

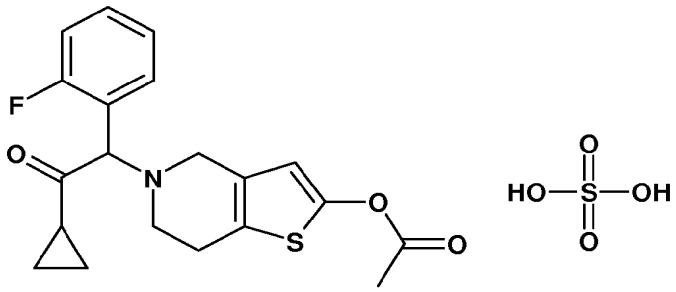


Figure A: Prasugrel hydrogensulfate

Prasugrel has an asymmetric carbon atom. The present invention covers the racemic form of Prasugrel hydrogensulfate as well as the individual stereoisomers and their mixtures.

Crystalline form I of Prasugrel hydrogensulfate can be prepared by

(a) heating a mixture of Prasugrel or a salt or a derivative thereof, sulfuric acid and optionally a solvent to a temperature of about 35 °C or more;

(b) reducing the temperature of the mixture to about 30 °C or below;

(c) adding seed crystals; and

(d) isolating crystalline form I of Prasugrel hydrogensulfate.

In step (a) a Prasugrel starting material is heated with sulfuric acid. The starting material can be Prasugrel itself or a salt thereof, in particular an acid addition salt of Prasugrel with an acid having a pKa of about 2 or more, such as the maleate salt, or another derivative thereof. Prasugrel, certain salts and derivatives can be prepared according to known procedures such as those mentioned in EP-A-542 411 or US-B-6,693,115.

Any suitable sulfuric acid can be used in step (a). Either diluted or concentrated sulfuric acid having a concentration in the range from about 5 to about 98 % can be employed. Preferably concentrated sulfuric acid, i.e. sulfuric acid having a concentration of about 95 to about 98 %, is used.

The ratio of Prasugrel to sulfuric acid can vary. Typically about 0.8 to about 5.0 equivalents, preferably about 0.9 to about 2.0 equivalents, more preferably about 1.0 to about 1.5, most preferably about 1.2 to about 1.5 equivalents of sulfuric acid to 1 equivalent of Prasugrel (mol : mol) will be employed.

The Prasugrel starting material and the sulfuric acid are optionally in admixture with a solvent. Any type of solvent can be employed as long as it does not adversely effect the formation of the desired crystalline form I. Examples of suitable solvents are ketones such as acetone, methyl ethyl ketone or diethyl ketone and esters such as ethyl acetate, propyl acetate and butyl acetate. The solvent is preferably selected from ketones. Acetone is the most preferred solvent.

The Prasugrel starting material is preferably used in a concentration in the range from about 30 to about 500 g/l, more preferably about 100 to about 250 g/l, most preferably in a concentration of about 125 g/l if a solvent is employed.

The mixture of Prasugrel starting material, sulfuric acid and the optional solvent is heated to a temperature of about 35 °C or more until all of the Prasugrel starting material has dissolved. The temperature at which the Prasugrel starting material is dissolved is typically from about 35 °C to about 60 °C, preferably from about 35 °C to about 40 °C in order to minimize degradation. If desired, the mixture can be stirred during the dissolution step.

Pure crystalline form I of Prasugrel hydrogensulfate can be prepared in the following manner. After the Prasugrel starting material has been dissolved, the temperature of the solution is reduced to about 30 °C or below, preferably about -25 to about 25 °C, more preferably about 0 to about 25 °C, most preferably about 0 to about 20 °C. The cooling of the solution will typically take from about 30 minutes to about 300 minutes, preferably about 60 to about 180 minutes. The reaction mixture can be agitated during the cooling step, if necessary.

It was found that crystalline form I of Prasugrel hydrogensulfate does not form easily unless seed crystals are present. Those seed crystals were only obtained by serendipity after

attempts to obtain a Prasugrel hydrogensulfate according to the general procedure of US 6,693,115 for the production of acid addition salts had failed.

In the process for the preparation of crystalline form I of Prasugrel hyrogensulfate, due to the cooling of the solution, crystals of form I of Prasugrel hydrogensulfate are able to grow after seeding. This is because at more elevated temperatures seed crystals might dissolve and Prasugrel hydrogensulfate might then remain in solution.

Seed crystals are added when the temperature of the solution has reached a value at which the seed crystals remain crystalline for a sufficiently long time, for example about 30°C or less, to facilitate crystallization. The seed crystals may be a pure crystalline form I of Prasugrel hydrogensulfate or may be Prasugrel hydrogensulfate seed crystals which can be prepared as set out in Example 1 of the present application.

The seed crystals obtained from example 1 are a mixture of amorphous Prasugrel hydrogensulfate and crystalline form I of Prasugrel hydrogensulfate.

After the temperature has been reduced to the desired temperature, the reaction mixture is left to stand at that temperature, so that crystallization can take place. The exact duration of the crystallization can vary. It will typically be from about 0.5 to about 48 hours, preferably from about 5 to about 24 hours. If desired, stirring can be conducted during this step, as long as the stirring is carried out in a manner which is gentle enough, so that it does not interfere with crystallization.
To complete crystallization the suspension may be cooled optionally with stirring to about 0°C for about 0.5 to 24 hours.

After the crystallization, crystalline form I of Prasugrel hydrogensulfate can be isolated from the mixture. Any conventional method such as filtration, centrifugation or evaporation of the solvent can be employed. If necessary, the crystals can be purified further by recrystallization.

The obtained crystals are mostly agglomerated but some larger lath-shaped crystals are also observed. The lath-shaped particles range in length from about 40 µm to about 550 µm and in width from about 10 µm to about 100 µm.
The agglomerates mainly consist of smaller lath shaped crystals. The formation of lath shaped crystals is favoured by slow crystallization conditions, e.g at a very gently stirring rate. In addition, columns and needles are observed by fast crystallization conditions, e.g. by

a stirring speed of 250 rpm. The columns and needles typically range in length from about 10 µm to about 30 µm and in width from about 1 µm to about 5 µm. The crystals show birefringence in polarized light which proves their crystallinity.

The molar ratio of Prasugrel to hydrogensulfate in the crystals is about 1:1.

The crystalline form I of Prasugrel hydrogensulfate can be characterized by an X-ray powder diffraction pattern having peaks at 2-theta angles as shown in Table 1. A characteristic X-ray powder diffraction pattern of crystalline form I of Prasugrel hydrogensulfate is shown in Figure 1.

Table 1: X-Ray Powder Diffraction (XRPD) pattern of crystalline form I of Prasugrel hydrogensulfate

Angle [°2-theta ± 0.2°]	relative intensity [%]
9.2	91.0
13.1	19.0
13.9	100.0
14.8	25.1
16.0	17.1
17.0	50.8
17.7	45.4
18.9	28.4
19.7	27.7
21.2	28.7
22.7	73.7
25.1	18.2
28.0	30.0

Crystalline form I of Prasugrel hydrogensulfate may be also characterized by an infrared spectrum having characteristic bands at 1751, 1712, 1495, 1153, 1060, 858 and 774 cm^{-1}. A usual deviation for these bands is ± 2 cm^{-1}. A typical IR spectrum is shown in Figure 2.

Furthermore, crystalline form I of Prasugrel hydrogensulfate may be characterized by a Raman spectrum as well. Characteristic bands are present at 1616, 1510, 1444, 1289, 1231,

1194, 1021, 871, 812, 778, 709, 580 and 539 cm^{-1}. A usual deviation for these bands is ± 2 cm^{-1}. A typical Raman spectrum is shown in Figure 3.

The water content of crystalline form I of Prasugrel hydrogensulfate may vary from about 0.0 – 2.0 %, e.g. the water content is about 0 % when stored at about 2 % relative humidity at 25 °C and about 2.0 % when stored at about 50 % relative humidity at 25 °C.

The uptake of water up to a water content of about 2% does not induce a change of the polymorphic form. The polymorph I of Prasugrel hydrogensulfate is the most stable polymorphic form of Prasugrel Hydrogensulfate at a relative humidity between 0% relative humidity and 50% relative humidity.

Because of the stability properties of Prasugrel (susceptibility to hydrolysis and oxidation), it is advantageous to dry crystalline form I of Prasugrel hydrogensulfate to a preferred water content and to store it relatively dry.

Therefore, in one embodiment of the present invention, the crystalline form I of Prasugrel hydrogensulfate is preferably dried to a water content of less than 0.8%, more preferably to a water content of less than 0.5% and most preferably to a water content of about 0,3% or less and is preferably stored at a relative humidity of less than 30 % relative humidity, more preferably at about 20% relative humidity or less.

In another preferred embodiment the crystalline form I of Prasugrel hydrogensulfate is stored in inert gas as well known in the art, e.g. from WO2006/135605, in order to prevent from oxidation.

The control of moisture content and relative humidity is also advantageous for solid pharmaceutical forms, e.g. capsules, tablets or other solid forms comprising prasugrel hydrogensulfates form I.

The present invention therefore also provides processes for the preparation of pharmaceutical compositions comprising crystalline form I of Prasugrel hydrogensulfate and a means to keep the relative humidity at 30% or less during storage, to ensure that crystalline form I of Prasugrel hydrogensulfate is chemically stable.

The present inventors found ways to stabilize crystalline form I of Prasugrel hydrogensulfate during the formulation and storage process.

The present invention therefore also relates to a pharmaceutical composition comprising the crystalline form I of Prasugrel hydrogensulfate, wherein the crystalline form I of Prasugrel hydrogensulfate is stably present.

"Stably present" as defined herein means that even after storage of the pharmaceutical composition for 180 days, and preferably even after storage for two years, the crystalline form I of Prasugrel hydrogensulfate is still present as crystalline form I of Prasugrel hydrogensulfate after storage for the indicated period. Such compositions can be produced by avoiding humid conditions, such as high relative humidity of the air, during the formulation steps. Furthermore, the above-identified humid conditions are to be avoided during storage in order to preserve the pharmaceutical composition of the invention.

It is preferred that the pharmaceutical composition of the invention comprising the crystalline form I of Prasugrel hydrogensulfate exhibits an equilibrium relative humidity of below 30%, preferably of from 2% to 30%, more preferably of from 10% to 25%, preferably from 15% to 25%, and more preferably of about 20% or less, in particular more preferably of from 15% to 20% or from 5% to 15%, for at least 180 days, preferably for at least two years.

The equilibrium relative humidity of the pharmaceutical compositions comprising the crystalline form I of Prasugrel hydrogensulfate or of the crystalline form I of Prasugrel hydrogensulfate is measured by determining the relative humidity in % in the air above a test sample, e.g. a pharmaceutical composition of the invention comprising the crystalline form I of Prasugrel hydrogensulfate, after establishment of a humidity equilibrium in a closed system at a constant temperature according to the following method: the equipment used is the commercially available measuring chamber Rotronic AW-VC comprising a hygrometer of the type BT-RS1. The test sample, e.g. a pharmaceutical composition of the invention comprising the crystalline form I of Prasugrel hydrogensulfate, is filled into a sampling dish which is placed into the measuring chamber which has been thermostated to a temperature of 25 +/- 1 °C, said chamber is subsequently closed and sealed. After establishment of an equilibrium of the relative humidity which state is typically shown by the disappearance of a trend indication, the value of the relative humidity in % is read from the hygrometer. Relative humidity is defined as the equilibrium relative humidity of the pharmaceutical compositions as measured as herein described. Filling of the chamber is to be performed in such a way as to provide complete filling of said chamber according to the instructions of the manufacturers. In case the test sample is a powder or granules for oral suspension, or a liquid suspension, said sample is directly placed into the above mentioned sampling dish. In case the test sample is a capsule, the appropriate number of capsules are opened and their contents is filled into the sampling dish. In case the test sample is a tablet, the appropriate number of tablets is

crushed by using a mortar, and filled into the sampling dish. In cases where the equilibrium humidity is expected to be below 30% or about 20 % or less, the above described preparation of the test samples before measurement and the measurement itself as herein described is to be performed in a glove box being equipped with a hygrometer wherein a relative humidity of about 5% is to be established by e.g. flushing with dried air or nitrogen. The above described method for measurement of the equilibrium relative humidity of the pharmaceutical compositions of the invention is herein also called ERH method.

The pharmaceutical composition of the present invention comprising the crystalline form I of Prasugrel hydrogensulfate is preferably stored in a relatively dry environment, and preferably it is to be assured that the storage environment remains relatively dry during the lifetime of the pharmaceutical composition.

The invention therefore also relates to a container comprising a pharmaceutical composition of the invention comprising the crystalline form I of Prasugrel hydrogensulfate, which container is capable to keep the equilibrium relative humidity of the composition at below 30%, preferably at below 20%, in particular more preferably of from 15% to 20% or from 5% to 15%, for at least 180 days, more preferably for at least two years. This can be achieved, for example, by use of a tightly sealed container, or by equipping the container with a means to keep the composition relatively dry.

Such a drying means may be, for example, desiccant bags, e.g. as commercially available under the trade name MINIPAX and containing 2 g of molecular sieve 4 Angstrom; or desiccant canisters, e.g. as available under the trade name SORBIT and containing 1 g Silicagel; desiccant capsules, e.g. as available under the trade name DRICAP, and containing 0.9 g Silicagel, or desiccant stoppers containing 2 g Silicagel.

The products or intermediate products obtained in the various steps of herein described processes are preferably stored at an environmental relative humidity of below 30%. Said products may thus be stored in aluminium barrels or drums, in so-called Nirosta® drums, such as commercially available as Müller® drums. Said drums may be made gas-tight, e.g. air-tight by applying a sealing means, such as sealing rings to the lid thereof. Said products may also be stored in containers made of aluminium or Nirosta®-material as mentioned above whereof the closures or lids are provided with a sealing means, such as a sealing ring.

The pharmaceutical compositions of the invention comprising the crystalline form I of Prasugrel hydrogensulfate are preferably packaged or filled into containers as herein described at an environmental relative humidity of below 30%, preferably at 20% or less.

Subsequently, said containers are tightly closed as herein described. Preferably, said containers are used for stable storage of the pharmaceutical compositions of the invention, for example at room temperature, such as at a temperature of about 20°C to 30°C, e.g. at about 25°C, for a prolonged period, e.g. for at least 6 months, preferably at least about 24 months, e.g. for up to at least 24 months, e.g. for up to at least about 30 months, such as for up to about 60 months.

A preferred container is a bottle, in particular a glass bottle, having e.g. a screw closure, or is a blister, e.g. an aluminum blister or strip, e.g. a blister consisting of 2 aluminum foils or strips, or may be any other suitable container. More preferably said container is a gas-tight container, such as an air-tight container.

Preferred containers are glass bottles sealed with an aluminum membrane, alu-alu-blisters or strips.
The container according to the invention is obtained by filling the pharmaceutical compositions of the invention into said container under the conditions as herein described.

Therefore, the present invention also relates to a container as described above, wherein the container in combination with the drying means is capable of maintaining the equilibrium relative humidity of the pharmaceutical composition of the invention comprising the crystalline form I of Prasugrel hydrogensulfate therein comprised at below 30%, preferably at about 20% or less, for at least 6 months, preferably for at least two years. In a preferred embodiment the container further encloses a gaseous atmosphere with a relative humidity of below 30%, preferably of about 20% or less. Equipping the container with a dry gaseous atmosphere, for example dry air or dry nitrogen gas, can be performed as known in the art. Preferred combinations of container and drying means are canisters or glass bottles with desiccant stoppers.

As mentioned above, special care as to the relative environmental humidity and as to the equilibrium relative humidity of the composition has to be taken during the production of pharmaceutical compositions of the invention comprising crystalline form I of Prasugrel hydrogensulfate.

Therefore, the present invention also relates to a process for preparing a pharmaceutical composition of the invention comprising the crystalline form I of Prasugrel hydrogensulfate comprising the steps of

a) mixing the crystalline form I of Prasugrel hydrogensulfate with one or more pharmaceutically acceptable excipients at a relative humidity of below 30%, preferably at about 20% or less;

b) optionally granulating the mixture obtained in step a) at a relative humidity of below 30%, preferably at about 20% or less; and

c) further processing the mixture obtained in step a) or the granulate obtained in step b) at a relative humidity of below 30%, preferably at about 20% or less, to obtain a pharmaceutical composition of the invention comprising the crystalline form I of Prasugrel hydrogensulfate.

It is preferred that the obtained pharmaceutical composition of the invention exhibits an equilibrium relative humidity of below 30%, preferably of from 10% to 25%, more preferably of about 20% or less, in particular more preferably of from 5% to 15% or of from 15% to 20%.

The mixture obtained from step a) or the granulate obtained from step b) as described above is preferably processed into an oral dosage form, like a capsule or a tablet, or granules for oral suspension, or a powder for oral suspension.

In a preferred embodiment, the obtained pharmaceutical composition comprising the crystalline form I of Prasugrel hydrogensulfate having an equilibrium relative humidity of below about 30%, preferably of about 20% or less, is filled into a container capable of maintaining the equilibrium relative humidity of the pharmaceutical composition at below 30%, preferably at about 20% or less, for at least 6 months, for examples the containers mentioned above, which may optionally further comprise a drying means sufficient to maintain the equilibrium relative humidity of the pharmaceutical composition at below 30%, preferably at about 20% or less.

As explained above, proper storage conditions for the pharmaceutical compositions of the invention comprising the crystalline form I of Prasugrel hydrogensulfate are important for maintaining the compositions in the desired form. Thus, the present invention further relates to the use of a container capable of maintaining a gaseous atmosphere at a relative humidity of below 30%, preferably at about 20% or less, for at least 6 months for storage of a pharmaceutical composition of the invention. Further, the present invention relates to the use of a gaseous atmosphere having a relative humidity of below 30%, preferably at about 20% or less, to stabilize the crystalline form I of Prasugrel hydrogensulfate.

The pharmaceutical compositions of the invention comprising the crystalline form I of Prasugrel hydrogensulfate may further comprise one or more pharmaceutically acceptable

excipients which are preferably selected from the group consisting of fillers, sweeteners, buffering agents, glidants, flowing agents, fllavoring agents, lubricants, preservatives, surfactants, wetting agents, binders, disintegrants and thickeners. Other excipients known in the field of pharmaceutical compositions may also be used. Furthermore, the pharmaceutical compositions may comprise a combination of 2 or more excipients also within one of the members of the above mentioned group. Preferably, the fillers are also sweeteners.

After the pharmaceutical compositions of the invention have been filled into the herein mentioned containers, said containers are preferably tightly closed, e.g. tightly or hermetically sealed, e.g. in a way to prevent any gaseous atmosphere from diffusing through the walls and/or closure of said containers. Methods of tightly sealing and/or closing said containers are known, such as sealing of glass bottles by applying an aluminium membrane to the bottle opening of said bottle by induction sealing and by applying a closure, e.g. a screw closure, or such as sealing of alu-alu blisters or strips by heat sealing according, e.g. analogously to known methods.

Within said preferably tightly sealed container comprising a gaseous atmosphere, preferably air, having a relative humidity of below 30%, preferably of about 20% or less, is maintained stable for at least 6 months, preferably at least 24 months. Thereby, the crystalline form I of Prasugrel hydrogensulfate comprised in the pharmaceutical compositions of the invention is stabilized in its form as herein defined over a period of at least 6 months, preferably for at least 24 months, such as for about 36 months.

Thus, the present invention also provides the use of a container capable of maintaining a gaseous atmosphere at a relative humidity of below 30%, preferably of about 20% or less, for at least 6 months for storage of a pharmaceutical composition of the invention comprising the crystalline form I of Prasugrel hydrogensulfate.

In a further aspect, the invention provides a pharmaceutical composition comprising crystalline form I of Prasugrel hydrogensulfate being obtainable by the processes as herein described preferably under the conditions as herein described with regard to starting material, relative humidity and further processing. Furthermore, said pharmaceutical compositions may be packaged and/or stored under the conditions and for the time period as herein described.

Unless otherwise indicated, the temperature applied during the herein described processes is preferably room temperature, e.g. is a temperature of about 20°C to about 30°C, such as about 25°C.

The present inventors have surprisingly found that Prasugrel hydrogensulfate possesses a higher solubility over a broad pH range from about pH 1.0 up to about pH 8.0, which reflects the pH-range in the stomach and the intestine in humans compared to other salts of Prasugrel, such as the hydrochloride or maleate salts. As bioavailability depends, among others, on solubility, an optimal active substance for oral application should show a high solubility in a broad pH-range. The solubility of various Prasugrel salts was determined according to the European Pharmacopoeia 6.0, 5.11 (2008) and is given in Table 2. Table 2 shows that the crystalline form I of Prasugrel hydrogensulfate is freely soluble in each of the different pH-media, whereas Prasugrel hydrochloride is only sparingly soluble at pH 1.2 and insoluble at pH 4.5 and in water. Prasugrel maleate is very slightly soluble at pH 1.2 and insoluble at pH 4.5 and in water.

Table 2: Solubility of various Prasugrel acid addition salts

Prasugrel	Hydrochloric acid medium pH 1.2	Acetate buffer pH 4.5	water
hydrogensulfate	freely soluble	freely soluble	freely soluble
maleate	very slightly soluble	insoluble	insoluble
hydrochloride	sparingly soluble	insoluble	insoluble

The crystalline form I of Prasugrel hydrogensulfate according to the present invention can be employed to treat or prevent any of the disorders which can be treated by Prasugrel or any of the other salts of Prasugrel. It is envisaged that it can also be employed to treat disorders which are indicated for the related compound Clopidogrel.

In particular, crystalline form I of Prasugrel hydrogensulfate can be used for treating or preventing a disorder selected from the group consisting of thrombosis, embolism, coagulation induced vascular diseases and recurrence thereof and for use as an adjunct to percutaneous coronary intervention procedures. Examples of coagulation induced vascular diseases and recurrence thereof are myocardial infarction, angina, pulmonary embolism, transient ischemic attack, deep vein thrombosis, thrombotic re-occlusion subsequent to a coronary intervention procedure, heart surgery or vascular surgery, peripheral vascular thrombosis, vascular diseases associated with diabetes mellitus, and/or Syndrome X (metabolic syndrome), heart failure, vascular complications of diabetes, and a disorder in which a narrowing of at least one coronary artery occurs. Preferably crystalline form I of Prasugrel hydrogensulfate can be used for preventing atherothrombotic events after

myocardial infarction, after stroke, in patients having established peripheral arterial disease or in patients having Acute Coronary Syndrome. Prasugrel hydrogensulfate form I is a suitable form especially for acute indications mentioned in the last sentence where the anti-platelet action of the active substance should start as fast as possible. High solubility increases the dissolution rate which leads to faster absorption of the active substance into the blood and therefore to a faster onset of the anti-platelet activity.

Crystalline form I of Prasugrel hydrogensulfate can be administered alone or in combination with other pharmaceutically active compounds such as acetyl salicylic acid. The crystalline form I of Prasugrel hydrogensulfate and the other pharmaceutically active compound can be administered either simultaneously or sequentially.

The formulation of crystalline form I of Prasugrel hydrogensulfate is not particularly limited and it can be formulated according to known principles, e.g. either alone or together with pharmaceutically acceptable carriers, excipients, diluents and the like.

The crystalline form I of Prasugrel hydrogensulfate can be administered according to any appropriate route. Typically it will be administered orally or parenterally, preferably orally. Preferred formulations are liquid aqueous preparations for oral use (e.g. oral solutions, oral emulsions, oral suspensions, powders and granules for oral solutions and suspensions, oral drops, powder for oral drops, syrups, powders and granules for syrups), soluble tablets and parenteral preparations (e.g. injections, for example subcutaneous injections, infusions, concentrates for injections or infusions, powders for injections or infusions, gels for injections, implants).

Typical formulations and indications for Prasugrel are described, for example, in US 6,693,115, WO 2006/135605, WO 2007/024472, US 2007/0203157, EP-A-1 310 245, WO 97/17064, US 2007/0003628, WO 2005/048992, and WO 2007/113857. In those references relating to Clopidogrel, it is to be understood that Clopidogrel is to be replaced by the crystalline form I of Prasugrel hydrogensulfate according to the present invention. It is to be noted that these patents and patent applications are given as an example only and that this list is not to be considered exhaustive.

As mentioned above, compared to other salts of Prasugrel, such as the hydrochloride or maleate salts, the Prasugrel hydrogensulfate of the present invention possesses a higher solubility over a broad pH range from about pH 1.0 up to about pH 8.0, which reflects the pH-range in the stomach and the intestine in humans.

The present invention is illustrated in the following examples, which should not be construed as limiting.

EXAMPLES

The powder diffractogram was collected on a Unisantis XMD 300 X-ray powder diffractometer with a position sensitive detector in parallel beam optics using the following acquisition conditions: tube anode: Cu, 40 kV, 0.8 mA; 3 – 43° theta/2-theta; simultaneous detection of regions of 10° per step with detector resolution 1024, counting time 300 seconds per step. A typical precision of the 2-theta values is in the range of ± 0.2° 2-theta. Thus a diffraction peak that appears at 5.0° 2-theta can appear between 4.8 and 5.2° 2-theta on most X-ray diffractometers under standard conditions.

The infrared spectrum was collected on a diamond ATR cell with an Bruker Tensor 27 FTIR spectrometer with 4 cm^{-1} resolution. A typical precision of the wavenumber values is in the range of ± 2 cm^{-1}. Thus an infrared peak that appears at 1716 cm^{-1} can appear between 1714 and 1718 cm^{-1} on most infrared spectrometers under standard conditions.

The Raman spectrum was collected with a BRUKER Senterra Raman spectrometer microscope at ambient conditions using a 785 nm laser. The sample (crystal) was brought to focus with a 20x long working distance objective. Then the spectrum was collected at 9 – 12 cm^{-1} resolution. A typical precision of the wavenumber values is in the range of about ± 2 cm^{-1}. Thus, a Raman peak that appears at 1716 cm^{-1} can appear between 1714 and 1718 cm^{-1} on most Raman spectrometers under standard conditions.

For determining the water content of crystalline form I of Prasugrel hydrogensulfate the moisture sorption isotherm aquired using a SPS11 moisture sorption analyzer (MD-Messtechnik, G_Ulm) using teflon pans was analyzed. The measurements were started at 40% relative humidity and decreased in 10% steps down to 0% relative humidity and then increased up to 50% relative humidity. The equilibrium condition for each step was set to a mass-constancy of ± 0,001% over 35 min.

Example 1: Preparation of seed crystals

1 ml ethyl acetate was added to 1.2 eq. (18 µl) concentrated sulfuric acid (95-97 %) and the solution was stirred at room temperature. After the addition of 100.0 mg Prasugrel a sticky coagulated mass of amorphous Prasugrel hydrogensulfate was obtained. The solvent was removed and the solid was dried under vacuum at room temperature for 2 hours. This material was added to a solution of 1.2 eq. (18 µl) concentrated sulfuric acid (95-97 %) and 100.0 mg Prasugrel in 800 µl acetone. The solution was stored without stirring for about 20 hours at -25 °C to grow white to off-white crystals. The solvent was removed and the crystals were dried under vacuum at room temperature to obtain a mixture of amorphous Prasugrel hydrogensulfate and crystalline form I of Prasugrel hydrogensulfate.

It should be noted that in an initial experiment the time required to obtain seed crystals was significantly longer, in the order of about three weeks. However, the procedure described in example 1 now provides seed crystals after the indicated 20 hour incubation.

Repeated cycles of the above procedure wherein a small amount of the obtained mixture was additionally added as a seed material to the Prasugrel / acetone / sulfuric acid solution further increased crystallinity of the obtained Prasugrel hydrogensulfate until 145.0 mg of Prasugrel hydrogensulfate form I seed crystals were obtained.

Example 2: Preparation of form I of Prasugrel hydrogensulfate

250.0 mg Prasugrel and 1.2 eq. (44 µl) concentrated sulfuric acid (95 – 97 %) were dissolved in 2 ml acetone at 40 °C. The solution was slowly cooled down to room temperature and Prasugrel hydrogensulfate seed crystals obtained in Example 1 were added. After 17.5 hours stirring at room temperature, the precipitate was filtered off, washed with acetone and dried at room temperature under vacuum to obtain 199.1 mg (63 % yield) of crystalline form I of Prasugrel hydrogensulfate.

Example 3: Preparation of form I of Prasugrel hydrogensulfate

200.0 mg Prasugrel maleate was slurried in 4 ml acetone at 60 °C. After the addition of 1.2 eq. (28 µl) concentrated sulfuric acid (95-97 %) a solution was obtained. The solution was then cooled down to 0-5 °C and Prasugrel hydrogensulfate seed crystals obtained in Example 1 were added. After 3 hours of stirring at 0-5 °C the precipitate was filtered off, washed with acetone and dried at room temperature under vacuum to obtain 96.9 mg (50 % yield) of crystalline form I of Prasugrel hydrogensulfate.

Example 4: HPLC analysis

Assay calculated as Prasugrel hydrogensulfate: 97.3 %

HPLC conditions	
Column	YMC-Hydrosphere C18, 150×4.6 mm, S-3 µm
Mobile phase A	H_2O/amidosulfonic acid (1000 g/3.884 g)
Mobile phase B	acetonitrile/H_2O/amidosulfonic acid (588 g/250 g/3.884 g)
Injection volume	7 µl
Flow rate	0.8 ml/min
Oven temperature	40 °C
Detection	UV 254 nm

The Prasugrel hydrogensulfate of the present invention may be used in the following formulation examples, which should not be construed in any way to be limiting.

The materials of the following formulations are to be combined before direct compression is performed to obtain 5 mg Prasugrel tablets (6.30 mg Prasugrel hydrogensulfate).

Formulation 1

Prasugrel hydrogensulfate	6.30 mg (equivalent to 5.00 mg base)
Lactose monohydrate	133.28 mg
Corn starch	23.42 mg
Highly disperse SiO_2	2.50 mg
Stearic acid	4.50 mg
Total	170.00 mg

Formulation 2

Prasugrel hydrogensulfate	6.30 mg (equivalent to 5.00 mg base)
Mannitol	109.86 mg
Cellulose microcrystalline	46.84 mg
Highly disperse SiO_2	2.50 mg
Stearic acid	4.50 mg
Total	170.00 mg

Formulation 3

Prasugrel hydrogensulfate	6.30 mg (equivalent to 5.00 mg base)
Lactose anhydrous	84.65 mg
Cellulose microcrystalline	80.80 mg
Glyceryl dibehenate	8.25 mg
Total	180.00 mg

Formulation 4

Prasugrel hydrogensulfate	6.30 mg (equivalent to 5.00 mg base)
Lactose anhydrous	70.89 mg
Cellulose microcrystalline	67.07 mg
Glyceryl dibehenate	8.25 mg
Pregelatinised starch	27.49 mg
Total	180.00 mg

Formulation 5

Prasugrel hydrogensulfate	6.30 mg (equivalent to 5.00 mg base)
Lactose anhydrous	62.65 mg
Cellulose microcrystalline	80.80 mg
Glyceryl dibehenate	8.25 mg
Pregelatinised starch	13.75 mg
Talc	8.25 mg
Total	180.00 mg

Formulation 6

Prasugrel hydrogensulfate	6.30 mg (equivalent to 5.00 mg base)
Lactose anhydrous	76.40 mg
Cellulose microcrystalline	67.05 mg
Glyceryl dibehenate	8.25 mg
Hydroxypropyl cellulose	13.75 mg
Talc	8.25 mg
Total	180.00 mg

Formulation 7

Prasugrel hydrogensulfate	6.30 mg (equivalent to 5.00 mg base)
Lactose anhydrous	76.40 mg
Cellulose microcrystalline	67.05 mg
Glyceryl dibehenate	8.25 mg
Crospovidone	13.75 mg
Talc	8.25 mg
Total	180.00 mg

Formulation 8

Prasugrel hydrogensulfate	6.30 mg (equivalent to 5.00 mg base)
Lactose anhydrous	97.70 mg
Methylcellulose 15CPS	34.00 mg
Crospovidone	24.00 mg
Magnesium stearate	7.60 mg
Colloidal silicon dioxide	0.40 mg
Total	170.00 mg

Formulation 9

Prasugrel hydrogensulfate	6.30 mg (equivalent to 5.00 mg base)
Lactose anhydrous	97.70 mg
Methylcellulose 15CPS	34.00 mg
Crospovidone	24.00 mg
Calcium stearate	7.60 mg
Colloidal silicon dioxide	0.40 mg
Total	170.00 mg

Formulation 10

Prasugrel hydrogensulfate	6.30 mg (equivalent to 5.00 mg base)
Lactose anhydrous	97.70 mg
Methylcellulose 15CPS	34.00 mg
Crospovidone	24.00 mg
Zinc stearate	7.60 mg

Colloidal silicon dioxide	0.40 mg
Total	170.00 mg

Formulation 11

Prasugrel hydrogensulfate	6.30 mg (equivalent to 5.00 mg base)
Lactose anhydrous	97.70 mg
Methylcellulose 15CPS	34.00 mg
Crospovidone	24.0 mg
Sodium stearyl fumarate	7.60 mg
Colloidal silicon dioxide	0.40 mg
Total	170.00 mg

Formulation 12

Prasugrel hydrogensulfate	6.30 mg (equivalent to 5.00 mg base)
Lactose anhydrous	97.70 mg
Methylcellulose 15CPS	34.00 mg
Crospovidone	24.0 mg
Stearic acid	17.60 mg
Colloidal silicon dioxide	0.40 mg
Total	180.00 mg

The following are further embodiments of the present invention:

1. Crystalline form I of Prasugrel hydrogensulfate having an X-ray powder diffraction pattern comprising peaks at 2-theta angles of 9.2 ± 0.2°, 13.1 ± 0.2°, 13.9 ± 0.2°, 14.8 ± 0.2°, 16.0 ± 0.2°, 17.0 ± 0.2°, 17.7 ± 0.2°, 18.9 ± 0.2°, 19.7 ± 0.2°, 21.2 ± 0.2°, 22.7 ± 0.2°, 25.1 ± 0.2° and 28.0 ± 0.2°.

2. The crystalline form I of Prasugrel hydrogensulfate according to 1 having an X-ray powder diffraction pattern substantially in accordance with Figure 1.

3. Crystalline form I of Prasugrel hydrogensulfate having an infrared spectrum comprising peaks at wavenumbers of 1751 ± 2 cm^{-1}, 1712 ± 2 cm^{-1}, 1495 ± 2 cm^{-1}, 1153 ± 2 cm^{-1}, 1060 ± 2 cm^{-1}, 858 ± 2 cm^{-1} and 774 ± 2 cm^{-1}.

4. The crystalline form I of Prasugrel hydrogensulfate according to 3 having an infrared spectrum substantially in accordance with Figure 2.

5. Crystalline form I of Prasugrel hydrogensulfate having a Raman spectrum comprising peaks at wavenumbers of 1616 ± 2 cm^{-1}, 1510 ± 2 cm^{-1}, 1444 ± 2 cm^{-1}, 1289 ± 2 cm^{-1}, 1231 ± 2 cm^{-1}, 1194 ± 2 cm^{-1}, 1021 ± 2 cm^{-1}, 871 ± 2 cm^{-1}, 812 ± 2 cm^{-1}, 778 ± 2 cm^{-1}, 709 ± 2 cm^{-1}, 580 ± 2 cm^{-1} and 539 ± 2 cm^{-1}.

6. The crystalline form I of Prasugrel hydrogensulfate according to 5 having a Raman spectrum substantially in accordance with Figure 3.

7. The crystalline form I of Prasugrel according to any one of 1 to 6 having a water content of less than 0.8%.

8. A process for the preparation of crystalline form I of Prasugrel hydrogensulfate comprising the steps of:
   (a) heating a mixture of Prasugrel or a salt or a derivative thereof, sulfuric acid and optionally a solvent to a temperature of about 35 °C or more;
   (b) reducing the temperature of the mixture to about 30 °C or below;
   (c) adding seed crystals; and
   (d) isolating crystalline form I of Prasugrel hydrogensulfate.

9. A pharmaceutical composition comprising crystalline form I of Prasugrel hydrogensulfate as defined in any one of embodiments 1 to 7 and optionally a pharmaceutically acceptable carrier.

10. The pharmaceutical composition according to 9 which is to be administered orally.

11. The pharmaceutical composition according to 9 or 10 for inhibiting blood platelet aggregation.

12. The pharmaceutical composition according to 9 or 10 for treating or preventing a disorder selected from the group consisting of thrombosis, embolism, coagulation

induced vascular diseases and recurrence thereof and for use as an adjunct to percutaneous coronary intervention procedures.

13. The pharmaceutical composition according to 12 wherein the coagulation induced vascular diseases and recurrence thereof are selected from the group consisting of myocardial infarction, angina, pulmonary embolism, transient ischemic attack, deep vein thrombosis, thrombotic re-occlusion subsequent to a coronary intervention procedure, heart surgery or vascular surgery, peripheral vascular thrombosis, vascular diseases associated with diabetes mellitus, and/or Syndrome X (metabolic syndrome), heart failure, vascular complications of diabetes, and a disorder in which a narrowing of at least one coronary artery occurs.

14. The pharmaceutical composition according to 9 or 10 for preventing atherothrombotic events after myocardial infarction, after stroke, in patients having established peripheral arterial disease or in patients having Acute Coronary Syndrome.

15. Crystalline form I of Prasugrel hydrogensulfate as defined in any one of 1 to 7 for use as a medicament.

16. Use of crystalline form I of Prasugrel hydrogensulfate as defined in any one of 1 to 7 for inhibiting blood platelet aggregation.

17. Use of crystalline form I of Prasugrel hydrogensulfate as defined in any one of 1 to 7 for the preparation of a medicament for treating or preventing a disorder selected from the group consisting of thrombosis, embolism, coagulation induced vascular diseases and recurrence thereof and for use as an adjunct to percutaneous coronary intervention procedures.

18. Use of crystalline form I of Prasugrel hydrogensulfate as defined in any one of 1 to 7 for the preparation of a medicament for preventing atherothrombotic events after myocardial infarction, after stroke, in patients having established peripheral arterial disease or in patients having Acute Coronary Syndrome.

19. A method of inhibiting blood platelet aggregation by administering a therapeutically effective amount of crystalline form I of Prasugrel hydrogensulfate as defined in any one of 1 to 7 to a patient in need thereof.

20. A method of treating or preventing a disorder selected from the group consisting of thrombosis, embolism, coagulation induced vascular diseases and recurrence thereof and for use as an adjunct to percutaneous coronary intervention procedures by administering a therapeutically effective amount of crystalline form I of Prasugrel hydrogensulfate as defined in any one of 1 to 7 to a patient in need thereof.

21. A method of preventing atherothrombotic events after myocardial infarction, after stroke, in patients having established peripheral arterial disease or in patients having Acute Coronary Syndrome by administering a therapeutically effective amount of crystalline form I of Prasugrel hydrogensulfate as defined in any one of 1 to 7 to a patient in need thereof.

22. A pharmaceutical composition comprising crystalline form I of Prasugrel hydrogensulfate according to any one of 1 to 7, wherein the equilibrium relative humidity of the composition is below 30%.

23. The pharmaceutical composition of 22, wherein the equilibrium relative humidity of the composition is about 20% or less.

24. A container comprising a pharmaceutical composition according to 22 and a means to keep the equilibrium relative humidity of the composition at below 30%.

25. The container of 24, wherein the container in combination with the means to keep the equilibrium relative humidity of the composition at below 30% is capable of maintaining the equilibrium relative humidity of the composition at below 30% for at least 6 months.

26. The container of 24 or 25, wherein the container further encloses a gaseous atmosphere with a relative humidity of below 30%.

27. A process for preparing a pharmaceutical composition according to 22 comprising the steps of

a) mixing crystalline form I of Prasugrel hydrogensulfate according to any one of 1 to 7, with one or more pharmaceutically acceptable excipients at a relative humidity of below 30%;

b) optionally granulating the mixture obtained in step a) at a relative humidity of below 30%; and

c) further processing the mixture obtained in step a) or the granulate obtained in step b) at a relative humidity of below 30 % to obtain a pharmaceutical composition according to claim 22.

28. The process of 27, wherein the mixture or granulate is processed into an oral dosage form.

29. The process of 28, wherein the oral dosage form is a capsule or a tablet.

30. The process of any one of 27 to 29 comprising the additional step of filling the obtained pharmaceutical composition having an equilibrium relative humidity of below 30% into a container capable of maintaining the equilibrium relative humidity of the pharmaceutical composition at below 30% for at least 6 months.

31. Use of a container capable of maintaining a gaseous atmosphere at a relative humidity of below 30% for at least 6 months for storage of a pharmaceutical composition according 22.

32. Use of a gaseous atmosphere having a relative humidity of below 30% to stabilize the crystalline form I of Prasugrel hydrogensulfate according to any one of 1 to 7.

CLAIMS

1. Crystalline form I of Prasugrel hydrogensulfate having an X-ray powder diffraction pattern comprising peaks at 2-theta angles of 9.2 ± 0.2°, 13.1 ± 0.2°, 13.9 ± 0.2°, 14.8 ± 0.2°, 16.0 ± 0.2°, 17.0 ± 0.2°, 17.7 ± 0.2°, 18.9 ± 0.2°, 19.7 ± 0.2°, 21.2 ± 0.2°, 22.7 ± 0.2°, 25.1 ± 0.2° and 28.0 ± 0.2°.

2. Crystalline form I of Prasugrel hydrogensulfate having an infrared spectrum comprising peaks at wavenumbers of 1751 ± 2 cm^{-1}, 1712 ± 2 cm^{-1}, 1495 ± 2 cm^{-1}, 1153 ± 2 cm^{-1}, 1060 ± 2 cm^{-1}, 858 ± 2 cm^{-1} and 774 ± 2 cm^{-1}.

3. Crystalline form I of Prasugrel hydrogensulfate having a Raman spectrum comprising peaks at wavenumbers of 1616 ± 2 cm^{-1}, 1510 ± 2 cm^{-1}, 1444 ± 2 cm^{-1}, 1289 ± 2 cm^{-1}, 1231 ± 2 cm^{-1}, 1194 ± 2 cm^{-1}, 1021 ± 2 cm^{-1}, 871 ± 2 cm^{-1}, 812 ± 2 cm^{-1}, 778 ± 2 cm^{-1}, 709 ± 2 cm^{-1}, 580 ± 2 cm^{-1} and 539 ± 2 cm^{-1}.

4. A process for the preparation of crystalline form I of Prasugrel hydrogensulfate comprising the steps of:
   (a) heating a mixture of Prasugrel or a salt or a derivative thereof, sulfuric acid and optionally a solvent to a temperature of about 35 °C or more;
   (b) reducing the temperature of the mixture to about 30 °C or below;
   (c) adding seed crystals; and
   (d) isolating crystalline form I of Prasugrel hydrogensulfate.

5. A pharmaceutical composition comprising crystalline form I of Prasugrel hydrogensulfate as defined in any one of claims 1 to 3 and optionally a pharmaceutically acceptable carrier.

6. The pharmaceutical composition according to claim 5 which is to be administered orally.

7. The pharmaceutical composition according to claim 5 or 6 for inhibiting blood platelet aggregation.

8. The pharmaceutical composition according to claim 5 or 6 for treating or preventing a disorder selected from the group consisting of thrombosis, embolism, coagulation

induced vascular diseases and recurrence thereof and for use as an adjunct to percutaneous coronary intervention procedures.

9. The pharmaceutical composition according to claim 5 or 6 for preventing atherothrombotic events after myocardial infarction, after stroke, in patients having established peripheral arterial disease or in patients having Acute Coronary Syndrome.

10. A pharmaceutical composition comprising crystalline form I of Prasugrel hydrogensulfate as defined in any one of claims 1 to 3, wherein the equilibrium relative humidity of the composition is below 30%.

11. Crystalline form I of Prasugrel hydrogensulfate as defined in any one of claims 1 to 3 for use as a medicament.

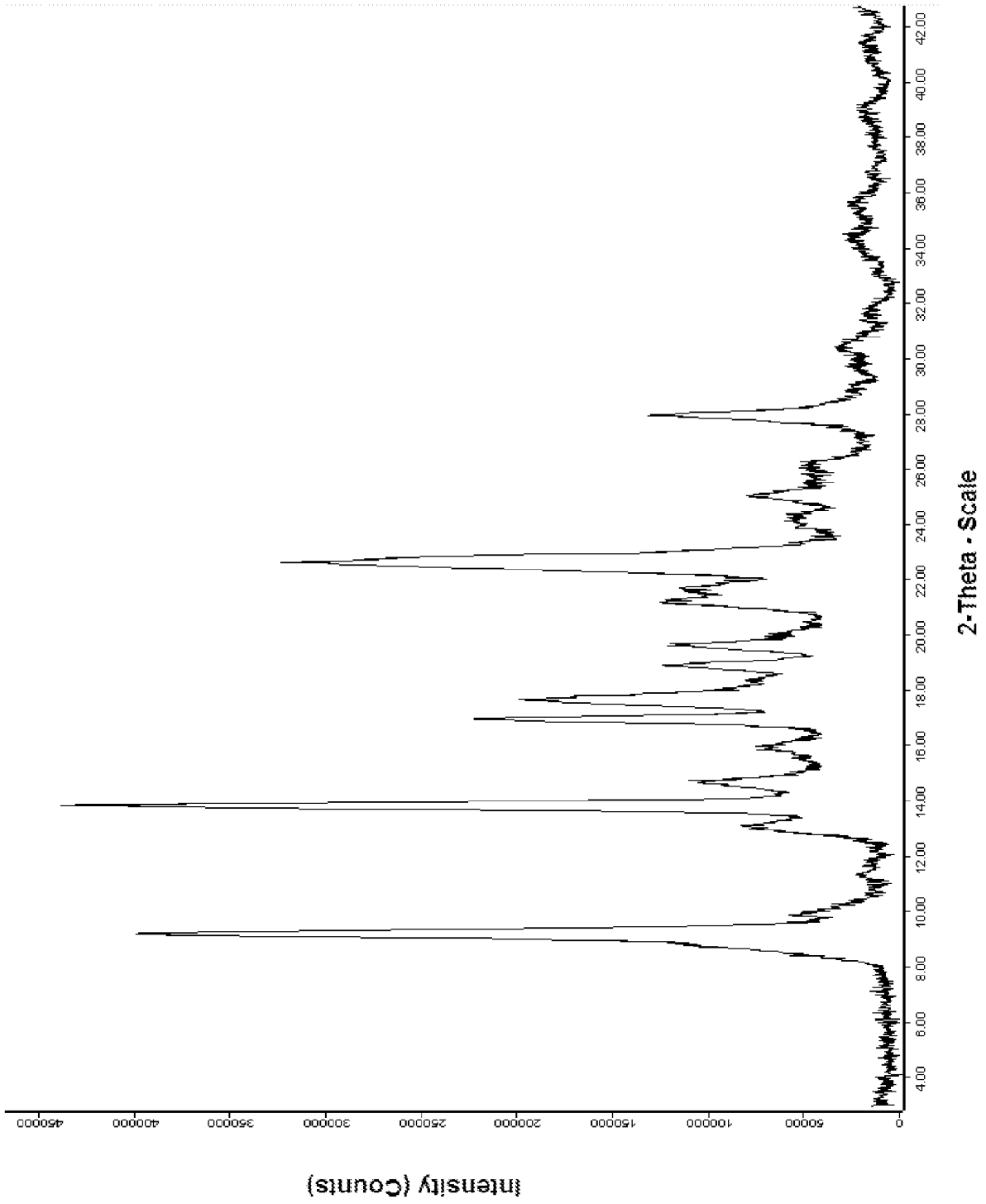
12. Use of crystalline form I of Prasugrel hydrogensulfate as defined in any one of claims 1 to 3 for inhibiting blood platelet aggregation.

13. A method of inhibiting blood platelet aggregation by administering a therapeutically effective amount of crystalline form I of Prasugrel hydrogensulfate as defined in any one of claims 1 to 3 to a patient in need thereof.

14. A method of treating or preventing a disorder selected from the group consisting of thrombosis, embolism, coagulation induced vascular diseases and recurrence thereof and for use as an adjunct to percutaneous coronary intervention procedures by administering a therapeutically effective amount of crystalline form I of Prasugrel hydrogensulfate as defined in any one of claims 1 to 3 to a patient in need thereof.

15. A method of preventing atherothrombotic events after myocardial infarction, after stroke, in patients having established peripheral arterial disease or in patients having Acute Coronary Syndrome by administering a therapeutically effective amount of crystalline form I of Prasugrel hydrogensulfate as defined in any one of claims 1 to 3 to a patient in need thereof.

Figure 1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250000
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2-Theta - Scale
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16.00
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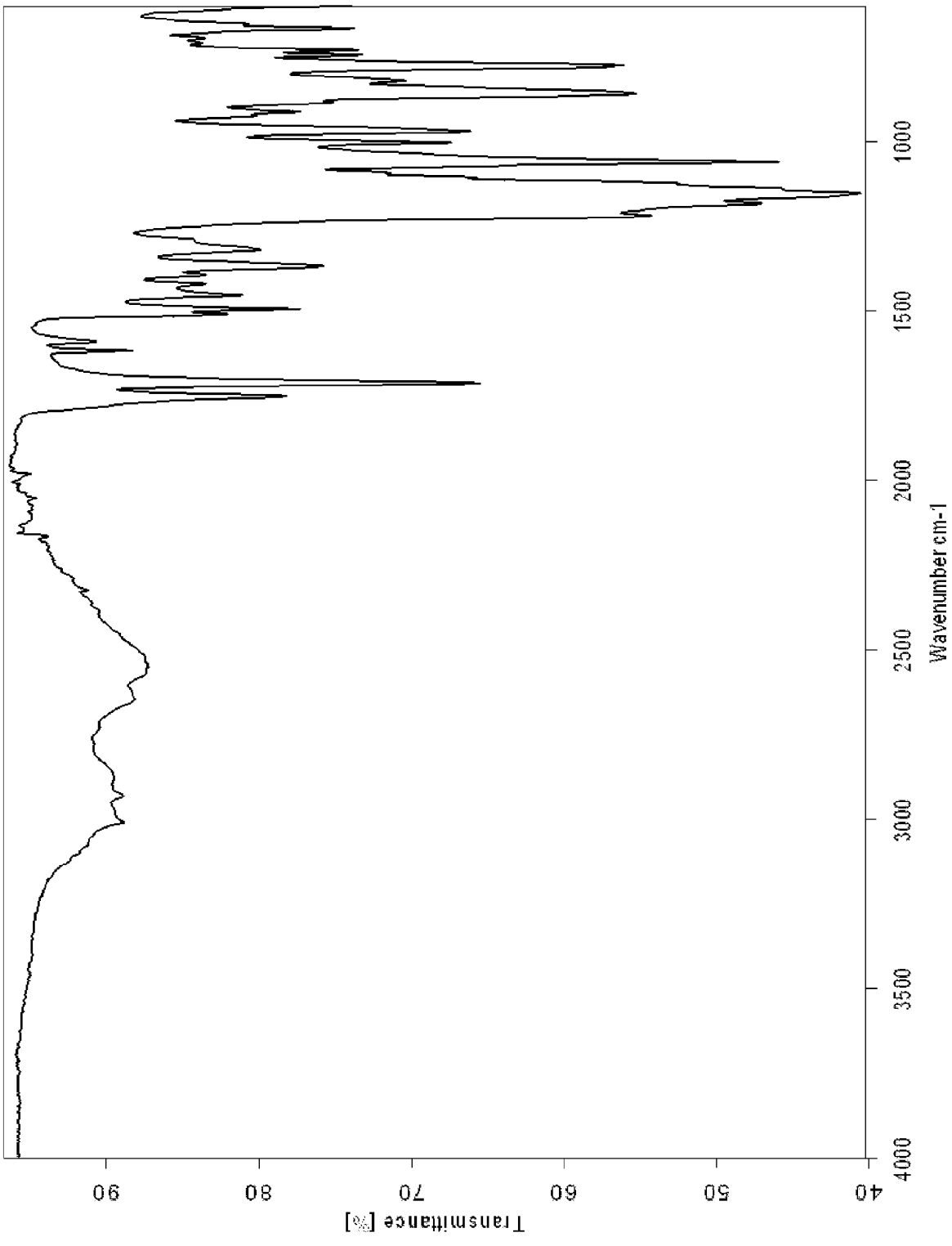
42.00

Figure 2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70
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50
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Wavenumber cm-1
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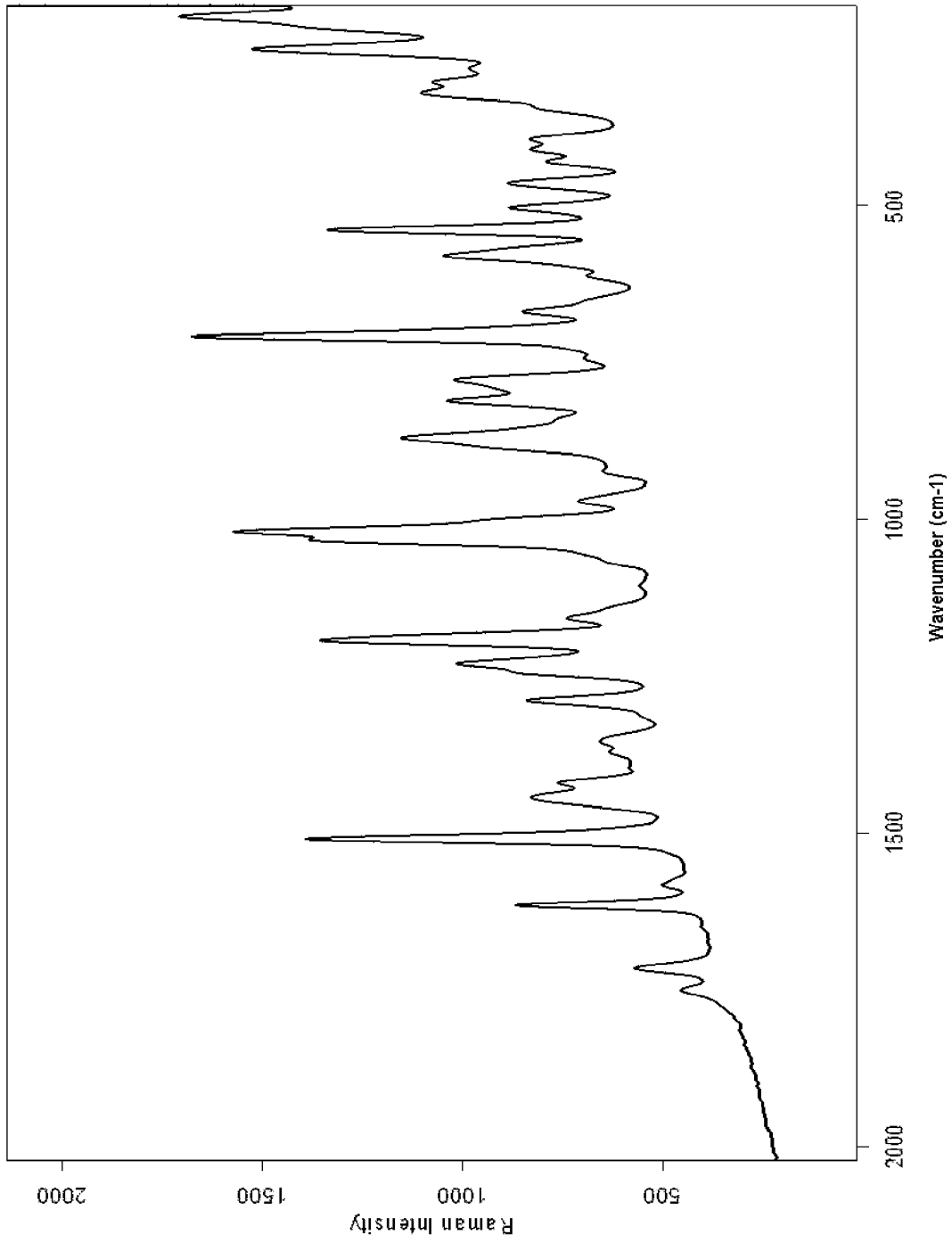
3500
3000
2500
2000
1500
1000

Figure 3


Raman Intensity
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1000
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2000
Wavenumber (cm-1)
500
1000
1500
2000

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/054914

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D495/04 A61K31/4365 A61P7/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 693 115 B2 (ASAI FUMITOSHI [JP] ET AL) 17 February 2004 (2004-02-17) cited in the application columns 5-7; examples 1-6 column 2, lines 3-10 column 4, lines 36-45 column 1, lines 48-59	1-15
A	WO 2007/114526 A (DAIICHI SANKYO COMPANY LTD [JP]; UBE INDUSTRIES; INOUE TERUHIKO; NAKAM) 11 October 2007 (2007-10-11) cited in the application abstract	1-15

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 August 2009	12/08/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Gutke, Hans-Jürgen

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2009/054914

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